# Transmission of Hand, Foot and Mouth Disease and Its Potential Driving Factors in Hong Kong, 2010-2014

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# Supplementary information

## Statistical methods

### Estimating effective reproduction number

*Statistical framework*

We estimated the daily effective reproduction number $R_s$ following the likelihood-based approach proposed by Cauchemez et al. [1], which is an extension of Wallinga and Teunis's method [2]. $n_s$ denotes the number of hand, foot and mouth (HFMD) cases showing symptoms on day $s$ and $X_s$ is the number of infectees of the $n_s$ cases. $R_s$ is then calculated as $X_s$ / $n_s$ according to the definition [3]. It is rare to observe $X_s$ directly, though it can be inferred from the observed epidemic curve and the serial interval distribution [2]. By considering the potential transmission networks as described by Wallinga et al. and Cauchemez et al. [1,2], the relative probability that cases with illness onset on day $k$ have been infected by cases with illness onset on day $s$ is

$$p_{ks} = \frac{(n_s - 1\{k = s\})w(k - s)}{\sum_{l \leq S}(n_l - 1\{k = l\})w(k - l)}$$

where $w(.)$ is the probability mass function of the serial interval distribution. In theory, a primary case and its infectee can show symptoms on the same day but a case cannot be infected by itself. Therefore, an indicator function $1\{\}$ was used to avoid counting the case itself as a potential primary case.

*Serial interval*

With limited studies on the serial interval of HFMD, we assumed the mean serial interval as 3.7 days (standard deviation 2.6 days) from the only available transmission study of enterovirus 71 in Taiwan [4]. We assumed a Weibull distribution for the serial interval as the distribution is not available from available studies. Different values and distributions of serial interval were used in the sensitivity analysis.

*Estimate daily count of HFMD cases*

According to a previous study, the case-hospitalization risk (CHR) of HFMD cases in Hong Kong ranged from 0.6% to 2.8% with an average of 1.3% between 2001 and 2009 [5]. We therefore assumed the CHR as a constant of 1.3% during our study period. Within the study period, weekly and daily population $P_t$ and $P_s$ were estimated by performing linear interpolation.

The daily incidence was first smoothed to capture the main trend of the reproduction number in Figure 1. In the main analysis, we derived the weekly cumulative incidence of hospitalizations ($C_t$) up to week *t* according to the relation:

$$C_t = \frac{\sum_1^t H_j}{P_t}$$

where $H_t$ is the cumulative sum of weekly count of hospitalization and $P_t$ is the weekly population in week *t*. Then we used cubic spline interpolation [6] to obtain the cumulative daily incidence of hospitalizations $C_s$. The daily incidence of hospitalizations $I_s$ on day *s* was calculated by $C_s - C_{s-1}$.

We derived the average incidence of hospitalizations $I_t$ in week $t$ according to the relation:

$$I_t = \frac{H_t}{P_t \times 7}$$

Cubic smoothing spline interpolation was used to obtain the daily incidence $I_s$ by minimizing the generalized cross validation score. The daily number of HFMD $n_s$ on day *s* was calculated by $n_s = I_s P_s / CHR$.

*Distribution of $R_t$*

Based on Cauchemaz's method [1], we first estimated $X_s$ which denotes the number of secondary cases infected by cases showing symptoms on day *s*. Considering the issue of right censoring, $X_s$ can be decomposed into cases showing symptoms on or before day S, $X_s^-(S)$, and cases showing symptoms after day *S*, $X_s^+(S)$. $X_s^-(S)$ follows a sum of Binomial distributions:

$$X_s^-(S) \sim \sum_{k \le S} Bin(n_{k,} p_{ks})$$

The expectation and variance of $X_s^-(S)$ therefore can be obtained by the followings:

$$E(X_s^-(S)) = \sum_{k \le S} n_k p_{ks}$$

$$Var(X_s^-(S)) = \sum_{k \le S} n_k p_{ks}(1 - p_{ks})$$

We assumed $X_s \sim Poisson(n_s l_s)$, where $l$ was given a a vague prior distribution $Gamma(10^{-5}, 10^{-5})$. $X_s^+(S)$ will then follow a Negative Binomial distribution:

$$X_s^+(S) \sim NB(X_s^-(S) + \alpha; \frac{n_s W_{sS} + \beta}{n_s + \beta})$$

where $W_{sS}$ is the cumulative probability that the generation interval is equal to or shorter than $S - s$.

Under the assumption that the $l$ has a vague prior, Cauchemez [1] derived an approximation for the expectation and variance of $X_s(S)$:

$$E(X_s(S)) \approx \frac{E(X_s^-(S))}{W_{sS}}$$

$$Var(X_s(S)) \approx \frac{Var(X_s^-(S))}{(W_{sS})^2} + \frac{1 - W_{sS}}{(W_{sS})^2} E(X_s^-(S))$$

Eventually, we obtained daily reproduction number $R_s$ simply according to the relation $R_s = X_s / n_s$. The weekly reproduction number $R_t$ was calculated as the geometric mean of $R_s$ within the corresponding week. The variance of $\log(R_t)$ was calculated using the following approximation by delta-method:

$$Var(R_t) \approx \left(\frac{R_t}{7}\right)^2 \sum_k \frac{Var(R_k)}{R_k^2}$$

where $R_k$ refers to the daily effective reproduction number for day *k*.

**Identification of the main epidemic periods**

We identified the main epidemic periods for each year starting from the exponential growth phase and ended by the last week of August (Figure 2). The exponential growth phase was defined as the period when the estimated daily number of HFMD kept growing and the growth rate ($\Delta n_s$) continuously increased for no less than two months at the beginning of an epidemic according to the basic feature of epidemics [7].

**Measurement of absolute humidity**

Absolute humidity ($AH$) reflects the actual content of water vapor in the air at a given temperature and was expressed as $g/m^3$ in the study. We derived daily $AH$ from relative humidity ($RH$, in percentage) and mean temperature ($F$, in Celsius) according to the following equation:

$$AH = c \times \frac{P_s(F) \times RH}{(F + 273.1) \times 100}$$

where $c$ is a consistant of 2.166824 $gK/\mathrm{J}$, which is approximately calculated from the molecular weight of water vapor over the gas content of water vapor. $P_s(F)$ refers to the saturation vapor pressure in $Pa$ given temperature $F$ and was calculated as [8]:

$$P_s(F) = 611.2 \times e^{\frac{17.67 \times F}{F + 243.5}}$$

Weekly absolute humidity was calculated as the arithmetic mean of daily $AH$ within the corresponding week.

**Linear regression model**

*Summary of the model*

We used a linear regression model proposed by te Beest et al [9] to explore the correlation between HFMD transmission and potential driving factors. Weekly effective reproduction number $R_t$ reflected HFMD transmissibility which depends on the potential factors including the depletion of susceptibles ($E$), absolute humidity ($AH$) and school vacations ($V$). We assumed $R_t$ is a function of the basic reproduction number $R_0$ according to the relation:

$$R_t = R_0 E_t AH_t^{\beta_{AH}} e^{\beta_V V_t}$$

where $\beta_{AH}$ and $\beta_V$ are the parameters of effects of absolute humidity and school vacations. After taking the between-year effect into account, the equation of linear regression was derived as [9]:

$$\log(R_{tj}) = \beta_{oj} + \beta_j C_{tj} + \beta_{AH} \log(AH_{tj}) + \beta_V V_{tj} + \varepsilon_{tj}$$

where $R_{tj}$ is the weekly effective reproduction number in week $t$ of year $j$; $\beta_{0j}$ is the intercept and equals to $\log(R_0 E_{0j})$ ($E_{0j}$ refers to the proportion of susceptibles in the beginning of year $j$); $\beta_j$ is the coefficients for the yearly depletion of susceptibles, which equals to -$c_j/E_{0j}$ ($c_j$ is a constant determined by the cumulative incidence of each year $j$); $C_{tj}$ is the cumulative incidence of HFMD cases up to week $t$-*1* of year $j$ (in scale of per 1 million); $AH_{tj}$ is the weekly mean absolute humidity; and $V_{tj}$ is a binary variable indicating whether the week is in school vacation or not.

We estimated the autocorrelation and partial autocorrelation of residuals from the fitted regression model without adjusting auto-correlation terms. The residuals from the model show autocorrelation (Supplementary Figure 3). We therefore fitted a model adding the autoregressive terms of reproduction numbers up to lag 2:

$$\log(R_{tj}) = \beta_{oj} + \beta_j C_{tj} + \beta_{AH} \log(AH_{tj}) + \beta_V V_{tj} + \beta_{AR1} \log(R_{(t-1)j}) + \beta_{AR2} \log(R_{(t-2)j}) + \varepsilon_{tj}$$

where $\beta_{AR1}$ and $\beta_{AR2}$ are the coefficients for the auto-regressive terms. $\varepsilon_{tj}$ is assumed to follow a normal distribution. The ACF and PACF plots did not indicate strong autocorrelation and partial autocorrelations after adjustment of autoregressive terms (Supplementary Figure 3). Results from the models with or without adjusting autocorrelation were very similar (Table 1-3, Supplementary Table 3), which suggests the autocorrelation in $R_t$ would not affect our main findings.

*Other meteorological factors*

We included absolute humidity as the meteorological factor in the main analysis. Previous studies reported temperature, relative humidity and air pressure positively correlated with the incidence of HFMD [10-12]. We therefore also included the above variables in the regression model but did not find significant associations with HFMD transmission, except for temperature in one model accounting for the autocorrelation of $R_t$ (results not shown). In fact, absolute humidity is highly correlated with temperature, relative humidity and air pressure (data not shown). We finally chose absolute humidity as it synthesizes all the above meteorological variables and the AIC and BIC scores suggested a good model fitness when including absolute humidity, comparing to model including other meteorological factors.

**Sensitivity analysis**

*Main epidemic periods*

We conducted a sensitivity analysis by defining other cutoffs for the main epidemic periods at the end of July, September and October respectively, in order to examine their potential impacts on the results. Models adjusting or without adjusting for autocorrelation were also fitted. The relative order of the potential driving factors were the same as our main results and the results did not suggest an association between absolute humidity and $R_t$, except for the case when the defined epidemic period ended early by the end of July (Table 3 and Supplementary Table 2). The definition of the main epidemic periods seems to have limited impacts on our main findings.

*EV71 activity*

EV71 was usually with higher case-hospitalization risks comparing to other serotypes in Hong Kong [5]. We therefore conducted a sensitivity analysis stratifying the study periods by EV71 activities. We defined the EV71 activity by comparing the proportion HFMD outbreaks attributed to EV71 in outbreaks associated with CA6, CA16 or EV71.

We defined the year 2010 and 2013 as lower EV71 activity years when EV71 was responsible for 4.4% and 11.3% of HFMD outbreaks while the year of 2011, 2012 and 2014 as the higher EV71 activity (accounting for 20.7% to 36.1% of the outbreaks) [13]. Models adjusting or without adjusting for autocorrelation were fitted. The relative importance of the potential driving factors were similar with our main results (Supplementary Table 3). No significant association between $R_t$, and absolute humidity was founded except for the case in years with lower EV71 activity and without adjusting autocorrelation (Supplementary Table 4). EV71 activity seems to have no impacts on our main findings.

*Serial interval*

A sensitivity analysis was also conducted assuming a serial interval with mean 7 days and 2 days respectively with a standard deviation of 2.6 days. Results from the sensitivity analysis indicate that a longer serial interval of HFMD would lead to larger estimated $R_t$ in the growth phase of the spring-summer epidemics (Supplementary Figure 1). The maximum values of $R_t$ during the exponential growth phase of spring-summer waves were estimated to be 1.17 to 1.26 in the study period. Assuming a mean serial interval of 2 days; while $R_t$ peaked at 1.42 to 1.60 when assuming the mean as 7 days (Supplementary Figure 1). A longer serial interval led to larger uncertainty in the $R_t$ estimates and slightly shortened the duration with estimated $R_t \geq 1$ (Supplementary Figure 1). We also estimated $R_t$ by assuming a Gamma or Lognormal distribution for the serial interval and found similar results as those assuming a Weibull distribution. Results were similar to our main analysis when $R_t$were estimated assuming different mean serial intervals.

*Case-hospitalization risk (CHR)*

We also estimated $R_t$ assuming a CHR of 0.6% and 2.8% respectively throughout the study period. Results indicate that the assumption on CHR would not affect the point estimate of $R_t$ and will result in narrower 95% confidence intervals for a lower CHR (Supplementary Figure 2). Assuming a stable CHR, data on hospitalizations provided consistent estimates of $R_t$, given the lack of outpatient information. However it may be challenging if the CHR changed substantially in a short period [14].

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## Supplementary Tables

**Supplementary Table 1.** Regression estimates of factors of HFMD transmission in Hong Kong adjusted by autocorrelation, 2010-14.

| Factors | Coefficient | 95% CI |
|---|---|---|
| **Yearly intercept** | | |
| 2010 | -0.08 | (-0.27, 0.11) |
| 2011 | 0.04 | (-0.01, 0.09) |
| 2012 | 0.01 | (-0.04, 0.05) |
| 2013 | 0.00 | (-0.04, 0.05) |
| 2014 | 0.00 | (-0.05, 0.04) |
| **Yearly depletion of susceptibles**† | | |
| 2010 | -0.03 | (-0.04, -0.02) *** |
| 2011 | -0.09 | (-0.13, -0.06) *** |
| 2012 | -0.06 | (-0.08, -0.03) *** |
| 2013 | -0.02 | (-0.03, -0.01) *** |
| 2014 | -0.07 | (-0.11, -0.04) *** |
| **Holiday** | | |
| No | ref | |
| Yes | 0.02 | (-0.01, 0.06) |
| **Absolute humidity** | 0.06 | (-0.01, 0.13) |
| $\mathbf{R_{AR1}}$ | 0.86 | (0.74, 0.98) *** |
| $\mathbf{R_{AR2}}$ | -0.67 | (-0.79, -0.55) *** |

*† Variable of cumulative incidence is in scale of 10-6.*

** P < 0.05; ** P < 0.01; *** P < 0.001*

*$R^2$ of the model is 0.77.*

**Supplementary Table 2.** Regression estimates of factors of HFMD transmission in Hong Kong using different ends of study period, 2010-14

| Factors | End by Jul | | End by Sep | | End by Oct | |
|---|---|---|---|---|---|---|
| | **Model A*** | **Model B†** | **Model A** | **Model B** | **Model A** | **Model B** |
| **Yearly intercepts** | | | | | | |
| 2010 | **-0.36 (-0.64, -0.07)** | -0.14 (-0.31, 0.02) | 0.16 (-0.12, 0.44) | 0.14 (-0.04, 0.31) | 0.10 (-0.12, 0.32) | 0.11 (-0.02, 0.25) |
| 2011 | 0.07 (0.00, 0.15) | 0.03 (-0.01, 0.08) | 0.05 (-0.03, 0.14) | 0.03 (-0.02, 0.08) | 0.04 (-0.03, 0.12) | 0.02 (-0.03, 0.07) |
| 2012 | 0.02 (-0.05, 0.09) | 0.02 (-0.02, 0.05) | 0.00 (-0.08, 0.08) | 0.00 (-0.05, 0.05) | 0.01 (-0.07, 0.08) | 0.00 (-0.05, 0.04) |
| 2013 | 0.00 (-0.08, 0.08) | 0.01 (-0.04, 0.05) | 0.04 (-0.04, 0.12) | 0.02 (-0.03, 0.08) | 0.03 (-0.05, 0.11) | 0.02 (-0.03, 0.07) |
| 2014 | 0.02 (-0.05, 0.10) | 0.00 (-0.03, 0.04) | 0.01 (-0.08, 0.09) | -0.01 (-0.06, 0.04) | 0.00 (-0.07, 0.08) | -0.01 (-0.05, 0.04) |
| **Yearly depletion of Susceptibles** | | | | | | |
| 2010 | **-0.05 (-0.08, -0.03)** | **-0.04 (-0.05, -0.02)** | **-0.01 (-0.03, 0.00)** | **-0.01 (-0.02, 0.00)** | **-0.02 (-0.03, -0.01)** | **-0.01 (-0.02, -0.01)** |
| 2011 | **-0.17 (-0.25, -0.10)** | **-0.10 (-0.14, -0.06)** | **-0.05 (-0.09, -0.01)** | **-0.04 (-0.06, -0.01)** | **-0.05 (-0.08, -0.02)** | **-0.03 (-0.05, -0.02)** |
| 2012 | **-0.11 (-0.15, -0.07)** | **-0.08 (-0.10, -0.05)** | -0.02 (-0.05, 0.01) | **-0.02 (-0.04, 0.00)** | **-0.03 (-0.05, -0.01)** | **-0.02 (-0.03, -0.01)** |
| 2013 | **-0.04 (-0.06, -0.02)** | **-0.03 (-0.04, -0.02)** | **-0.02 (-0.03, -0.01)** | **-0.01 (-0.02, -0.01)** | **-0.02 (-0.03, -0.01)** | **-0.01 (-0.02, -0.01)** |
| 2014 | **-0.16 (-0.22, -0.10)** | **-0.10 (-0.13, -0.06)** | -0.04 (-0.08, 0.00) | **-0.03 (-0.05, 0.00)** | **-0.04 (-0.07, -0.01)** | **-0.03 (-0.05, -0.01)** |
| **Holiday** | | | | | | |
| No | ref | ref | ref | ref | ref | Ref |
| Yes | 0.03 (-0.03, 0.08) | 0.01 (-0.02, 0.03) | -0.03 (-0.07, 0.01) | -0.02 (-0.05, 0.00) | -0.02 (-0.06, 0.02) | -0.02 (-0.05, 0.00) |
| **Absolute humidity** | **0.17 (0.07, 0.28)** | **0.09 (0.02, 0.15)** | -0.03 (-0.13, 0.08) | -0.02 (-0.09, 0.04) | 0.00 (-0.08, 0.08) | -0.01 (-0.06, 0.04) |
| **$R_{AR1}$** | NA | **0.87 (0.75, 0.98)** | NA | **0.88 (0.76, 1.00)** | NA | **0.89 (0.78, 0.99)** |
| **$R_{AR2}$** | NA | **-0.64 (-0.75, -0.54)** | NA | **-0.63 (-0.75, -0.51)** | NA | **-0.63 (-0.74, -0.52)** |
| **$R^2$ (%)** | 48.7 | 85.3 | 24.6 | 71.5 | 29.3 | 73.7 |

** Model A refers to model without considering autocorrelation while † Model B refers to model adjusting autocorrelation.*

*Estimates in bold format indicate statistical significant results with p-value < 0.05.*

**Supplementary Table 3.** Variance explained by factors of HFMD transmission in Hong Kong stratified by EV71 activity, 2010-14

| Driving factors | Lower EV71 activity[a] | | Higher EV71 activity[b] | |
|---|---|---|---|---|
| | Model A[*] | Model B[†] | Model A | Model B |
| **Susceptibles depletion** | 0.27 | 0.25 | 0.27 | 0.23 |
| **Between-year effects** | 0.03 | 0.02 | 0.05 | 0.01 |
| **Absolute humidity** | 0.05 | 0.00 | 0.00 | 0.01 |
| **Holidays** | 0.03 | 0.00 | 0.02 | 0.01 |
| **Total $R^2$** | 0.38 | 0.27 | 0.34 | 0.22 |

*a Years with lower EV71 includes 2010 and 2013 (EV71 accounted for 11.3% and 4.4% of the outbreaks).*

*b Years with higher EV71 includes 2011, 2012 and 2014 (EV71 accounted for 20.7-36.4% of the outbreaks).*

** Model A refers to model without considering autocorrelation.*

*† Model B used outcome variable $R_s^*$, which was modified by autocorrelation.*

**Supplementary Table 4.** Regression estimates of factors associated with HFMD transmission in Hong Kong stratified prevalence of EV71, 2010-14.

| Driving factors | Years with lower EV71[a] | | Years with higher EV71[b] | |
|---|---|---|---|---|
| | Model A[c] | Model B[d] | Model A | Model B |
| **Yearly intercept[a]** | | | | |
| 2010 | **-0.46 (-0.89, -0.02)** | -0.05 (-0.33, 0.23) | NA | NA |
| 2011 | NA | NA | 0.11 (-0.34, 0.56) | -0.08 (-0.38, 0.22) |
| 2012 | NA | NA | -0.07 (-0.17, 0.03) | -0.03 (-0.09, 0.03) |
| 2013 | -0.01 (-0.09, -0.07) | 0.01 (-0.04, 0.05) | NA | NA |
| 2014 | NA | NA | -0.07 (-0.16, 0.03) | -0.04 (-0.10, 0.02) |
| **Yearly depletion of susceptibles[†§]** | | | | |
| 2010 | **-0.05 (-0.08, -0.03)** | **-0.03 (-0.04, -0.01)** | NA | NA |
| 2011 | NA | NA | **-0.12 (-0.19, -0.06)** | **-0.10 (-0.15, -0.05)** |
| 2012 | NA | NA | **-0.06 (-0.10, -0.01)** | **-0.06 (-0.10, -0.03)** |
| 2013 | **-0.04 (-0.06, -0.02)** | **-0.02 (-0.03, -0.01)** | NA | NA |
| 2014 | NA | NA | **-0.09 (-0.15, -0.02)** | **-0.08 (-0.13, -0.04)** |
| **Holiday** | | | | |
| No | ref | ref | ref | ref |
| Yes | **0.08 (-0.01, 0.16)** | 0.00 (-0.05, 0.06) | 0.05 (-0.03, 0.13) | 0.04 (-0.01, 0.09) |
| **Absolute humidity ($g/m^3$)** | **0.21 (0.05, 0.37)** | 0.05 (-0.05, 0.16) | 0.03 (-0.13, 0.19) | 0.08 (-0.03, 0.19) |
| **$R_{AR1}$** | NA | **0.80 (0.62, 0.99)** | NA | **0.90 (0.73, 1.07)** |
| **$R_{AR2}$** | NA | **-0.64 (-0.81, -0.46)** | NA | **-0.72 (-0.91, -0.53)** |
| **$R^2$** | 0.38 | 0.27 | 0.34 | 0.22 |

*a Years with lower EV71 includes 2010 and 2013 (EV71 accounted for 11.3% and 4.4% of the outbreaks).*

*b Years with higher EV71 includes 2011, 2012 and 2014 (EV71 accounted for 20.7-36.4% of the outbreaks).*

*c Model A refers to model without considering autocorrelation.*

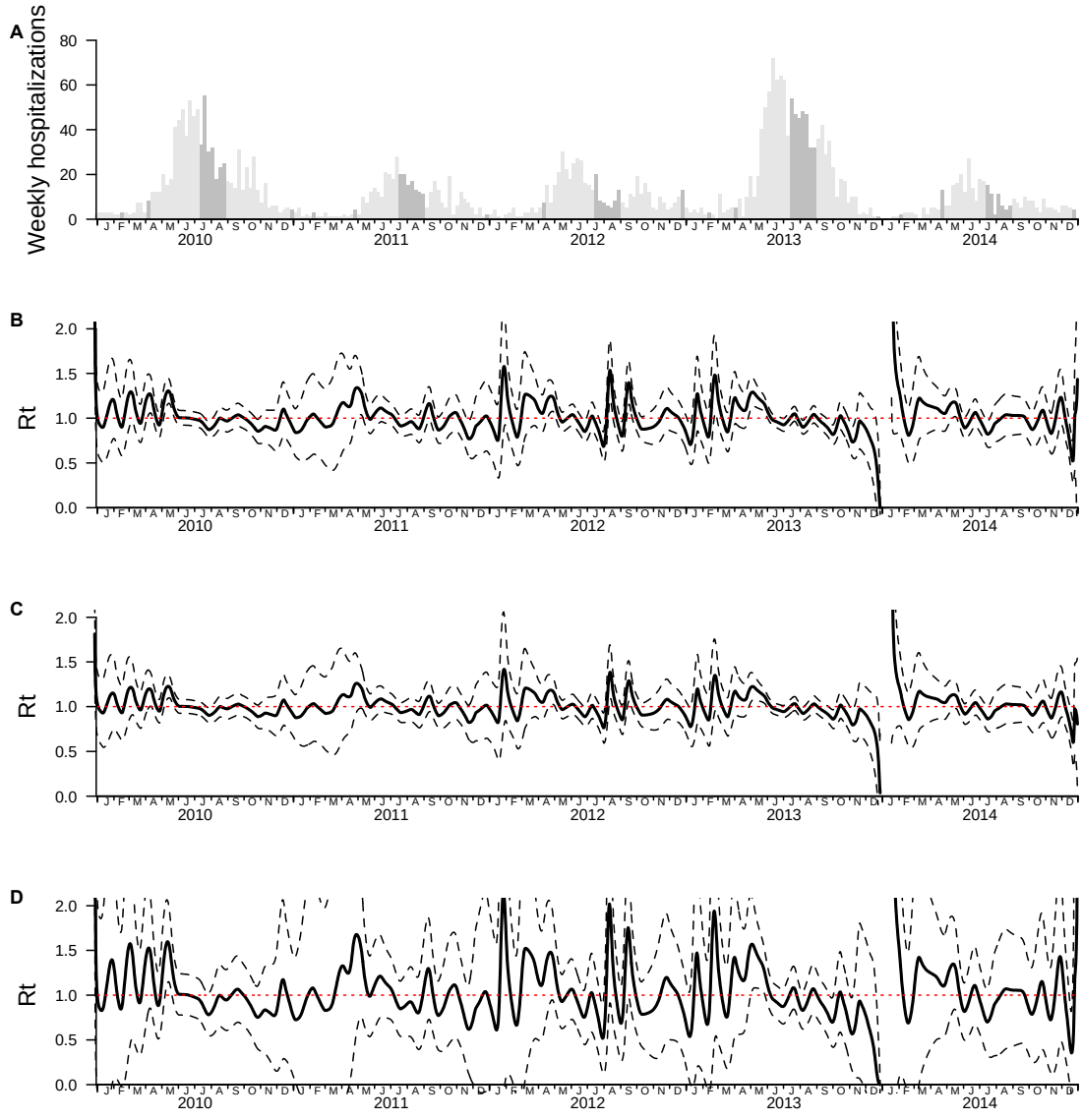
*d Model B used outcome variable $R_S^*$, which was modified by autocorrelation.*

*§ In the linear regression model, the coefficients for yearly intercept and yearly depletion of susceptibles both are compounds of the fraction of susceptibles at beginning of each year ($E_{0j}$), so there are in total five pairs of coefficients for yearly intercept and yearly depletion of susceptibles [23].*

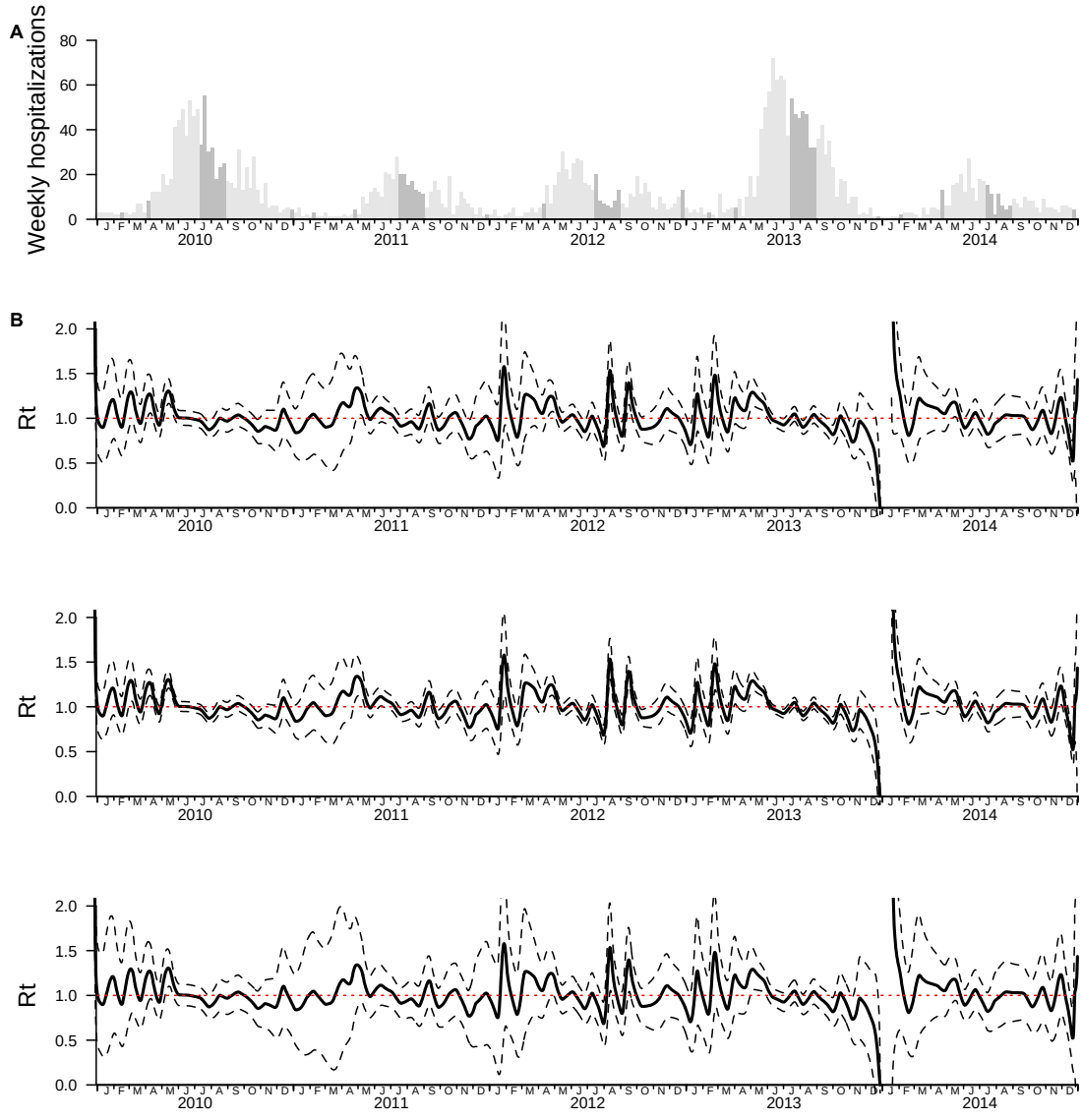
*† Variable of cumulative incidence is in scale of 10-6.*

## Supplementary Figures

**Supplementary Figure 1. Sensitivity analysis on length of serial interval.** A: Weekly number of hospitalized HFMD cases in Hong Kong from 1 Jan 2010 to 31 Dec 2014. B, C and D: Estimated daily $R_t$ with 95% confidence interval assuming serial interval with mean 3.7, 2 and 7 days respectively. The standard deviation was assumed to be 2.6 days for all situations. The dotted lines represent the threshold of $R_t$=1.



**Supplementary Figure 2. Sensitivity analysis on case-hospitalization risk (CHR).** A: Weekly number of hospitalized HFMD cases in Hong Kong from 1 Jan 2010 to 31 Dec 2014. B, C and D: Estimated daily $R_t$ with 95% confidence interval assuming CHR as 1.3%, 1.6% and 2.8% respectively. The dotted lines represent the threshold of $R_t$=1.



**Supplementary Figure 3. ACF and PACF of residuals of model fitted with or without adjusting autocorrelation.** Panel A and B, model without adjusting autocorrelation. Panel C and D, model after adjusting autocorrelation. The dashed lines represent the bounds of statistical significance.